Impact of Donor Characteristics and HLA Matching on Survival of Chinese Patients with Hematologic Malignancies Undergoing Unrelated Hematopoietic Stem Cell Transplantation

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We retrospectively analyzed the impact of donor characteristics and HLA matching on outcomes in Chinese patients undergoing unrelated hematopoietic stem cell transplantation (HSCT). A total of 693 patients with hematologic malignancies who underwent HSCT between 2005 and 2010 had available survival data at 100 days or 1 year posttransplantation in the Buddhist Tzu-Chi Stem Cell Center database. The overall survival rates at 100 days and 1 year were 83.3% and 65.2%, respectively. Mismatches of HLA-A, -B, and -DRB1 at the antigen or allele level, along with inadequate cell dose, were associated with a significant risk of mortality (hazard ratio [HR] = 2.36, $P < .001$; HR = 1.44, $P = .005$; and HR = 2.20, $P = .009$, respectively). In 107 donors with matched HLA-A, -B and -DRB1 and known HLA-C match status, 22.4% had an HLA-C antigen mismatch, resulting in an HR of 2.87 for mortality relative to complete 8/8 matches ($P = .005$). Recipients with unknown HLA-C match status also had a significantly worse outcome (HR = 1.73; $P = .039$). Multivariate analysis revealed that cell dose and HLA-A, -B, -C, and -DRB1 antigen match status significantly affected the final outcome of survival ($P = .012$ and $<.001$, respectively). Our data indicate that HLA-C match status should be confirmed before HSCT from an unrelated donor. Inadequate cell dose remains an important determinant of poor transplantation survival. Further studies to elucidate the importance of matching of specific HLA loci are needed to better understand the risk of HSCT and improve patient outcomes.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has been successfully applied to treat numerous malignant and nonmalignant hematologic diseases. The use of stem cells from HLA-matched unrelated volunteer donors (MUDs) is an accepted option for patients without a matching sibling donor, with comparable outcomes to matched sibling donor HSCT [1]. In Taiwan, MUDs account for approximately 25% of graft sources, and this percentage is increasing [2]. Although the benefits of HSCT are well established, the high incidence of complications associated with this procedure requires continued investigation to improve stem cell engraftment, reduce treatment toxicities, avoid graft-versus-host disease (GVHD), and increase the available pool of suitable donors.

The importance of HLA matching is well documented in unrelated donor HSCT [3-7]. Donor registry searches often identify multiple HLA-A, -B, and -DRB1 matched donors for a patient [8].

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Table 1. Patient Disease Summary Statistics

Disease (n = 693)	n (%)
Acute myelogenous leukemia	247 (35.6%)
Acute lymphoblastic leukemia	210 (30.3%)
Acute biphenotypic/nonspecific leukemia	13 (1.9%)
Chronic myelogenous leukemia	132 (19%)
Myelodysplastic syndrome	42 (6.1%)
Non-Hodgkin lymphoma	34 (4.9%)
Hodgkin's lymphoma	7 (1.0%)
Multiple myeloma	2 (0.3%)
Chronic lymphocytic leukemia	5 (0.7%)
Other hematologic malignancy	1 (0.1%)

Strategies for optimal unrelated donor selection vary. Transplant physicians often prefer donors who are HLA-C–matched, male, younger than other possible donors, seronegative for cytomegalovirus (CMV), and ABO-compatible [9-12]. Priority also may be given to female donors who are nulliparous [13] and donors who are racially matched with the patient. Most of these conclusions were derived from studies using data from Western patients. To date, no systemic analysis has been conducted regarding the effects of donor factors on the outcomes of MUD HSCT in Chinese individuals. A study of the effects of donor characteristics and HLA matching on transplantation outcomes in a Chinese population may lead to improved outcomes of MUD HSCT in the future.

In the present study, we examined the effects of various donor characteristics and HLA matching on outcomes in Chinese recipients of MUD allogeneic HSCT, focusing on the need for and impact of HLA-C matching. We analyzed the associations between overall survival and donor factors including age, ABO compatibility, sex, stem cell source, stem cell dose, and HLA matching in the patient–donor pairs recorded in the database of the Buddhist Tzu-Chi Stem Cell Center.

PATIENTS AND METHODS

We analyzed data from MUD HSCTs performed in Taiwan and China between January 2005 and December 2010 under the auspices of the Buddhist Tzu-Chi Stem Cell Center. All identifying donor and recipient information was removed before analysis. This study was approved by the Institutional Review Board of Tzu-Chi General Hospital. Patients with nonmalignant diseases were excluded from the study. A total of 790 donor–recipient pairs were available for 100-day and 1-year survival analysis, 693 of whom underwent HSCT for treatment of a hematologic malignancy. The patients received a variety of pretransplantation conditioning and GVHD prophylaxis regimens, with much of this information not available in the current dataset.

Various HLA typing methods were applied in different institutes; however, all of the donors and many of the recipients underwent molecular-based HLA typing at the Buddhist Tzu-Chi Stem Cell Center. Donors and recipients were considered allele-matched for a given locus when their high-resolution typing results were identical. Antigen-level disparity involved conversion of the 4-digit typing result back to its first 2 digits, with the exception of a few HLA-B alleles that were mapped to their corresponding serologic specificities.

The planned volume of harvested bone marrow (BM) was 20 mL/kg recipient body weight, with a minimal volume of 600 mL and a maximum volume of 20 mL/kg donor weight [14]. The target $CD34^+$ cell dose for mobilized peripheral blood stem cells (PBSCs) was 5×10^6 cells/kg recipient body weight. If the target $CD34^+$ cell dose was not met with the first apheresis, a second apheresis procedure was performed [15]. A cell dose inadequate for transplantation was defined as a total nucleated cell count $<2 \times 10^8$ cells/kg recipient weight for harvested BM or a $CD34^+$ cell count $<2 \times 10^6$/kg for mobilized PBSCs.

ABO-matched pairs had identical ABO blood groups. Major ABO mismatches were defined as the presence of antidonor isohemagglutinins in recipients, that is, transplantation from a non–type O donor to a type O recipient or from a type AB donor to a type A or B recipient. Minor ABO mismatches included the presence of antirecipient isohemagglutinins in donors, that is, transplantation from a type O donor to a non–type O recipient or from a type A or B donor to an type AB recipient. In the bidirectional mismatched group, both patients and donors had isoagglutinins directed against each other, that is, transplantation from a type A donor to a type B recipient or vice versa.

Characteristics of recipients and donors were described by summary statistics. Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Donor factors analyzed included age, sex, HLA matching, blood type matching, and stem cell dose. A Cox proportional hazards model was used for multivariate analysis of the effects of these donor factors and HLA matching on survival outcome. A P value $<.05$ was considered statistically significant. All tests were performed using MedCalc for Windows, version 9.6.0.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

In the 693 HSCT recipients with hematologic malignancies, the most common indications for transplantation were acute myelogenous leukemia (35.6%), acute lymphoblastic leukemia (30.3%), and chronic myelogenous leukemia (19.0%). Other indications are listed in Table 1. Median age was 26 years (range, 1-69 years) for the recipients and 30 years (range, 19-54 years) for the donors. Details of disease status were known for 236 recipients (34.1%) before transplantation, and 36 recipients (15.3%) were beyond second complete

Table 2. Log-Rank Test of the Effect of Donor Characteristics and HLA Matching on Overall Survival after Unrelated HSCT

	HR	95% CI	P
Antigen matching for 6 loci			
Match at HLA-A, -B, and -DRB1 (n = 626)	1		
Any mismatch at HLA-A, -B, or -DRB1 (n = 67)	2.36	2.11-5.71	<.001
Antigen matching for 8 loci			
Match at HLA-A, -B, -C, and -DRB1 (n = 83)	1		
Match at HLA-A, -B, and -DRB1 but unknown HLA-C status (n = 519)	1.73	1.02-2.40	.039
Match at HLA-A, -B, and -DRB1 but mismatch at HLA-C (n = 24)	2.87	1.50-10.15	.005
Any mismatch at HLA-A, -B, or -DRB1 (n = 67)	3.90	2.28-7.11	<.001
Allele matching for 6 loci			
Match at HLA-A, -B, and -DRB1 (n = 406)	1		
Any mismatch at HLA-A, -B, or -DRB1 (n = 282)	1.45	1.12-1.91	.005
Allele matching for 8 loci			
Match at HLA-A, -B, -C, and -DRB1 (n = 61)	1		
Match at HLA-A, -B, and -DRB1 but unknown HLA-C status (n = 329)	1.53	0.87-2.41	.158
Match at HLA-A, -B, and -DRB1 but mismatch at HLA-C (n = 16)	1.18	0.36-3.87	.779
Any mismatch at HLA-A, -B, or -DRB1 (n = 282)	2.11	1.14-2.84	.012
Cell dose			
Adequate (n = 675)	1		
Inadequate (n = 18)	2.20	1.34-7.75	.009
Source			
BM (n = 189)	1		
PBSCs (n = 504)	0.96	0.72-1.28	.792
Blood type			
ABO match (n = 269)	1		
Major ABO mismatch (n = 147)*	1.16	0.82-1.66	.398
Minor ABO mismatch (n = 203)†	1.05	0.76-1.44	.785
Bidirectional ABO mismatches (n = 61)‡	0.90	0.56-1.47	.686
Sex matching			
Female to female (n = 111)	1		
Male to male (n = 281)	1.31	0.88-1.88	.193
Male to female (n = 156)	1.25	0.80-1.93	.325
Female to male (n = 145)	1.32	0.85-2.03	.218
Donor age, years			
19-29 (n = 326)	1		
30-39 (n = 268)	1.09	0.82-1.45	.541
40-54 (n = 99)	1.31	0.90-2.00	.149

*Transplantation from a non–type O donor to a type O recipient or from a type AB donor to a type A or B recipient.
†Transplantation from a type O donor to a non–type O recipient or from a type A or B donor to a type AB recipient.
‡Transplantation from a type A donor to a type B recipient or vice versa.

remission or had another high-risk condition. Data on conditioning regimen were available for 203 recipients, 185 of whom (91.1%) received a myeloablative regimen. Allele typing data were unavailable for 5 recipients, and blood type data were unavailable for another 13 recipients.

A total of 107 HLA-A, -B, and -DRB1 antigen-matched donor–patient pairs had known HLA-C matching status; 24 (22.4%) were not matched at HLA-C. Fifteen of 76 donor–patient pairs (19.7%) who were matched at the HLA-A, -B, and -DRB1 allele level were mismatched at HLA-C. The median $CD34^+$ cell dose was 7.41×10^6 cells/kg for PBSC transplantation, and the median total nucleated cell count was 4.24×10^8 cells/kg for BM transplantation. Two of 189 BM transplants (1.1%) and 16 of 504 PBSC transplants (3.2%) met the criteria for an inadequate cell dose for transplantation.

The overall 100-day and 1-year survival rates were 83.3% and 65.2%, respectively. The log-rank test for the effect of donor characteristics on recipient survival times revealed a significant risk of mortality in recipients with any antigen or allele mismatch of HLA-A, -B, or -DRB1 (hazard ratio [HR] = 2.36, $P < .001$ and HR = 1.44, $P = .005$, respectively) (Table 2; Figure 1A and B). When the analysis incorporated the influence of HLA-C, recipients antigen-matched at HLA-A, -B, and -DRB1 but antigen-mismatched at HLA-C had an HR of 2.87 relative to those with a complete 8 of 8 match ($P = .005$) (Figure 1C). Unknown HLA-C antigen match status was also associated with a significant risk of mortality (HR = 1.73; $P = .039$). The HR was highest for any antigen mismatch at HLA-A, -B, or -DRB1 compared with an 8/8 match (HR = 3.9; $P < .001$). At the allele level, statistically significant differences in risk were observed between any mismatch at the HLA-A, -B, or -DRB1 locus relative to a complete 8/8 match (HR = 2.11; $P = .012$) (Figure 1D). This risk trend remained for HLA-C allele matching status, although it was not statistically significant.

Patients who received cell doses inadequate for transplantation had worse survival compared with those who received adequate cell doses (HR = 2.20; $P = .009$). Stem cell source, donor age, sex match, and blood type match did not affect overall survival rates (Table 2). Multivariate analysis using a Cox

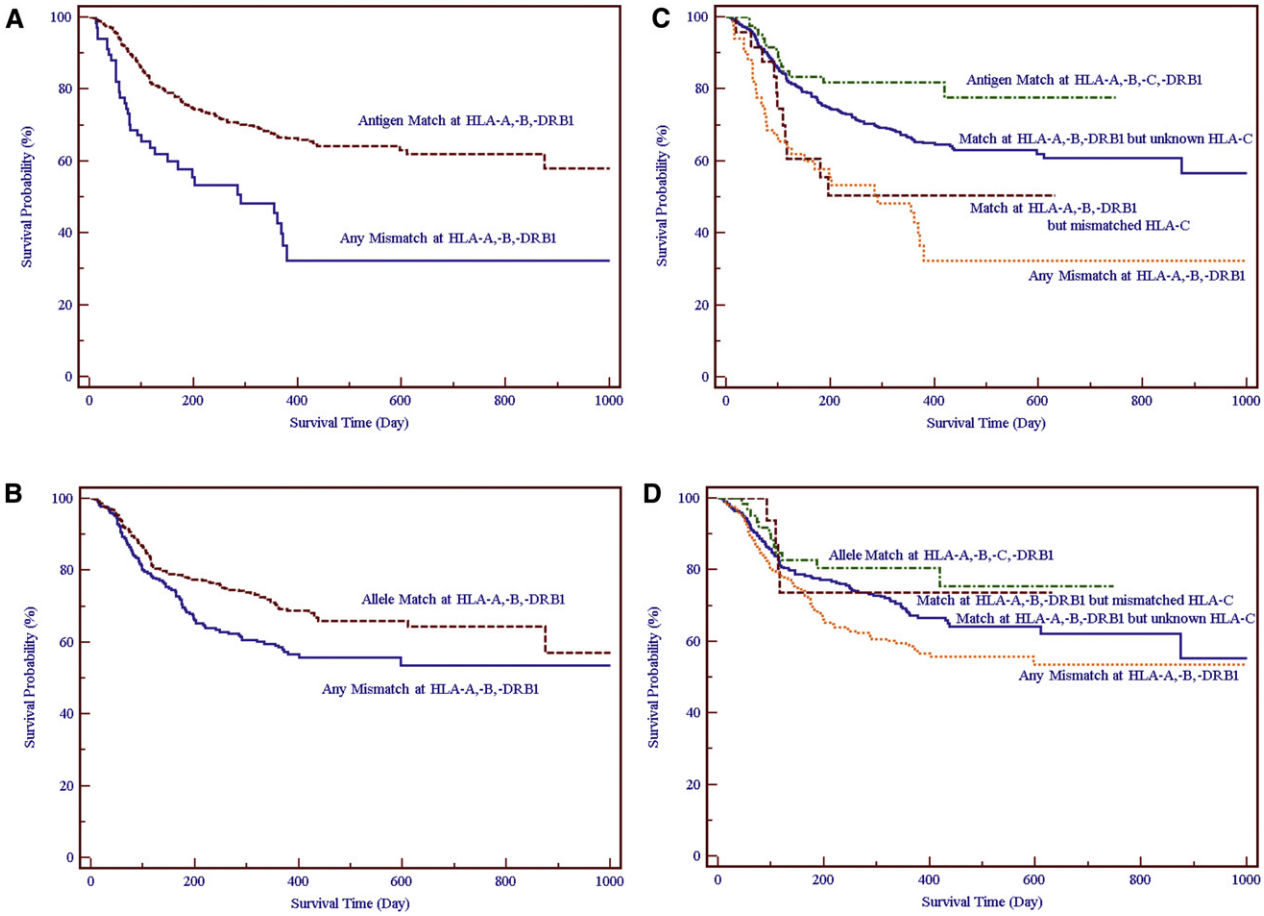

Figure 1. Overall survival rates according to HLA matching status. (A) Survival as an outcome for antigen matching at HLA-A, -B, or -DRB1. (B) Survival as an outcome for allele matching at HLA-A, -B, or -DRB1. (C) Influence of the presence of HLA-C matching, in addition to matching at HLA-A, -B, and -DRB1, at the antigen level. (D) The influence of the presence of HLA-C matching, in addition to matching at HLA-A, -B, and -DRB1, at the allele level.

proportional hazards regression model showed that cell dose and HLA-A, -B, -C, and -DRB1 antigen matching status significantly affected the final outcome of survival ($P = .012$ and $<.001$, respectively).

DISCUSSION

Although several previous large cohort studies have focused on the influence of donor factors and HLA matching on the outcome of unrelated HSCT, most of these data were derived from Western and Japanese populations. Here we describe for the first time the effects of donor factors and HLA matching status on outcomes in recipients of MUD HSCT in a Chinese population. Our results demonstrate the significant impact of HLA-A, -B, or -DRB1 mismatches at the antigen and allele levels on transplantation outcomes.

Previous studies have shown that mismatches at HLA-A or -DRB1 appeared to have a greater negative impact on survival compared with mismatches at HLA-B or -C [6,7]. Japanese studies reported no significant negative impact of HLA-C mismatch on overall survival [3,5]. These findings suggest that the impact of HLA-C on HSCT outcome may vary among different races. Most of the previous studies primarily evaluated HSCTs with BM as the stem cell source [4-7]. In the current National Marrow Donor Program files, >70% of adult donations are PBSCs [16]. A recent analysis of PBSC transplantation found that HLA-C antigen-level mismatch is more detrimental to survival [17]. This finding raises the possibility of a differential effect of HLA-C match on the outcomes of BM and PBSC transplantation. Given that PBSC transplants represented 72.7% of all HSCTs analyzed in the present study, we also observed a significant adverse effect of HLA-C match on survival outcome. This discordance of the impact of specific HLA matching among different stem cell sources and among different ethnic groups warrants further study.

Although our cohort was not large enough to allow us to analyze the effect of mismatches at each specific locus, our findings show a significant risk of mortality related to HLA-C antigen mismatch in short-term follow-up. The survival of HSCT recipients with HLA-C antigen mismatch was similar to recipients with any HLA-A, -B, or -DRB1 mismatch. In addition, ensuring that donor–recipient pairs match at HLA-A, -B, and -DRB1 while ignoring HLA-C status might

not adequately identify the risks associated with HSCT. Outcomes were significantly worse in recipients with unknown HLA-C status compared with HLA-C–matched recipients. HLA-C antigen mismatch was detected in 22.4% of recipient–donor pairs with matched HLA-A, -B, and -DRB1, even though the individuals were of the same ethnicity. These HLA-C mismatches were not related to linkage disequilibrium due to allelic mismatches at HLA-B; the percentage of HLA-C mismatches was similar in donor–recipient pairs with allele-matched HLA-A, -B, and -DRB1. The actual incidence of mismatch might be higher, given that some physicians may avoid HSCT after confirming an HLA-C mismatch. The observed survival trend remained with regard to allele matching status, although the power of these findings is limited by the small number of cases in the subgroups. Our findings suggest that determination of HLA-C status (at least at the antigen level) is critical to understanding the risk of MUD HSCT.

A recent study reported that 56% of patients will have ≥10 suitably HLA-matched adult donors in the current National Marrow Donor Program files [18]. Although some donor characteristics have been recognized as potential risk factors for transplantation outcome, several recent studies found no significant effects of donor factors on the survival of HSCT recipients, with the exception of donor age [9,19,20]. In the present study, no statistical differences in survival were associated with donor factors. This finding might reflect the relatively small impact of donor factors, such as age, sex, and ABO blood type matching, in contrast to the importance of HLA matching and stem cell dose.

Previous evidence has demonstrated that the cell dose is adversely correlated with transplantation outcome [21-24]. Although inadequate cell dose has been defined as $<2 \times 10^8$ nucleated cells in BM grafts and $<2 \times 10^6$ $CD34^+$ cells in mobilized PBSC grafts, the accurate incidence of inadequate cell dose and the actual risk associated with this factor are seldom reported. In previous studies, a significant percentage (27%-50%) of recipients received a relatively low BM cell dose ($2.4\text{-}2.6 \times 10^8$ cells/kg) [22,23], and approximately 18% of PBSC samples were found to have poor mobilization ($<20 \times 10^6$ $CD34^+$ cells/L) [25]. In the present study, 18 recipients (2.6%) had an inadequate cell dose (3.2% of PBSC donors and 1.1% of BM donors). The incidence of poor mobilizers in our study was comparable to that in a recent report of PBSC harvesting [26]. Despite the efforts of donor centers, procuring adequate cell doses remains a challenge in BM and PBSC collection. In the present study, survival HR was 2.20 (95% CI, 1.3-7.8; $P = .009$) in recipients with an inadequate cell dose. The possibility of inadequate cell dose and the associated risk for transplantation outcome should be incorporated into pretransplantation considerations. Our recent work suggests that some donor factors, including sex, higher body weight/body mass index, high preharvest WBC count, and younger age, might affect stem cell collection from different sources [15,27]. If concerns are raised about obtaining an adequate number of stem cells, then further consideration of donor characteristics might be helpful in selecting optimal donors, even though the donor characteristics do not directly affect transplantation outcome.

The major limitation of this study is insufficient data for recipients. Only 34.1% of the recipients had detailed information on disease status before transplantation. In addition, data on conditioning regimens and GVHD prophylaxis were unavailable for many recipients, and data on CMV status were not available in our database. Thus, we focused on the impact of donor factors in recent transplantation for hematologic malignancies between 2005 and 2010, to decrease the confounding effects of disease and treatment differences among individuals. For patients in the first or second complete remission, any antigen mismatch and any allele mismatch at HLA-A, -B, or -DRB1 were still significantly associated with poor outcome (Supplemental Table). Owing to our small number of patients, the impact of HLA-C status and inadequate cell dose did not reach significance in this subgroup analysis.

The primary mission of the Tzu-Chi Stem Cell Center (also known as the Tzu-Chi Marrow Donor Registry) is to provide a suitable donor for every patient in need of transplantation, and to ensure that stem cells are collected safely and in sufficient numbers for the recipient. We sought to clarify the effects of donor characteristics on stem cell donation and unrelated transplantation in our previous and current works [14,15,27-29]. Future collaborations with Chinese BM transplantation societies to further analyze long-term transplantation outcomes and the impact of recipient factors would greatly aid efforts to improve transplantation in Chinese individuals.

In conclusion, our study has revealed that in Chinese populations, HLA matching is an important factor influencing survival outcomes in MUD HSCT. We have also shown that the HLA-C locus plays a significant role in transplantation survival, necessitating verification before transplantation. Inadequate cell dose remains an important determinant of poor survival after MUD HSCT. Further studies investigating the impact of donor characteristics and matching of specific HLA loci on MUD HSCT outcomes in the Chinese population may aid optimal donor selection and ultimately improve outcomes in this population.

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SUPPLEMENTARY DATA

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